how well peripheral counts predicted CD34 recovery during the first collection, linear regression was performed using WBC, platelet (Plt) count, and PCD34 count as independent variables. Data were log transformed. WBC and Plt both were correlated with CD34 yield (p of slope = 0.000 and 0.012, respectively). However, coefficients of correlation (r^2) were low (0.137 and 0.162) rendering these parameters of little value for predicting the behavior of the individual patient. In contrast, the correlation of CD34 yield and PCD34 count was striking (r^2=0.958). Cross tabs analysis of PCD34 performed on the day of leukapheresis revealed that a cutoff of 10 PCD34/microliter gave a 92.6% probability of collecting in a single leukapheresis, and a 98.8% probability after 1 or more leukaphereses. We are using these data to construct an algorithm to schedule patients for leukapheresis, with particular attention to the difficult to mobilize patient.

GVH/GVL

13

ANTIGEN PRESENTING CELLS IN THE LIVER RECRUITE ACTIVATED ALLOGENEIC CD8+ T CELLS TO ELICIT HEPATIC GRAFT-VERSUS-HOST DISEASE

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Graft-versus-host disease (GVHD) induced by donor T cells recognizing minor histcompatibility antigens (miHAs) primarily target specific organs such as the liver, skin and intestine. We have previously demonstrated that rapid activation donor T cells by host antigen presenting cells (APCs) is sufficient to both activation and effector phases of acute GVHD. However, it is not well understood how these organs become the main targets of activated alloreactive T cells. In order to measure whether tissue resident APCs might play a critical role in initiating the local development of acute GVHD, we selectively depleted host macrophages and DCs from the livers and spleens but not from the skin, peripheral lymph nodes (PLN), or mesenteric lymph nodes (MLN) of C57BL/6 (B6) mice by intravenous administration of liposomal-chlodronate prior to allogeneic bone marrow transplantation. Depletion of host hepatic and splenic macrophages and DCs significantly inhibited the proliferation of donor C3H.SW CD8+ T cells in the spleen but not in the PLN or MLN of B6 mice. Such organ-selective depletion of host tissue APCs also markedly reduced the trafficking of allogeneic CD8+ T cells into the livers and spleens, but not PLN and MLN, of B6 recipients as compared to that of the control mice. Acute hepatic, but not cutaneous, GVHD was inhibited as well, resulting in improved survival of liposomal-chlodronate treated B6 recipients. When C3H.SW CD8+T cells were activated in normal B6 recipients, recovered and adoptively transferred into secondary B6 recipients, activated donor CD8+ T cells rapidly migrated into the livers and spleens of control B6 recipients, but was markedly decreased in B6 mice that were depleted of hepatic and splenic macrophages and DCs. Interestingly, host APC activation of donor T cells induced the expression of CCR5 followed by CCR1 and CCR4. In contrast, CCR7 that is expressed on naive T cells was dramatically reduced on these activated CD8+ T cells. Thus, tissue resident APCs control the local recruitment of allo-reactive donor T cells and the subsequent development of acute GVHD via the coordinated expression of chemokine receptor CCR7, CCR5 and CCR1 on activated donor CD8 T cells.

14

A PHASE I/II STUDY OF RECOMBINANT HUMAN KERATINOCYTE GROWTH FACTOR (KGF) IN PATIENTS WITH HIGH RISK HEMATOLOGIC MALIGNANCIES UNDERGOING MISMATCHED RELATED OR UNRELATED DONOR TRANSPLANT

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In murine BMT systems, the administration of KGF reduces small bowel damage and serum systemic inflammatory mediators resulting in less clinical GVHD while preserving GVL and improving leukemia free survival. We initiated a phase I/II, schedule escalation trial of KGF plus standard GVHD prophylaxis (tacrolimus and methotrexate) in patients with an unrelated or HLA mismatched donor who are therefore at high risk for developing acute GVHD (AGVHD). All study patients (n=11) had high risk hematologic malignancies. Patients received a full-intensity conditioning regimen of CVB (cyclophosphamide, VP-16, BCNU), BAC (busulfan, cytarabine, cyclophosphamide) or CyTBI (cyclophosphamide, TBI 1200 cGy). KGF (60 mcg/kg/day intravenously) was administered for 3 consecutive days prior to the conditioning regimen, and then for 3 consecutive days each week starting Day 0, escalating in 2 week blocks. One DLT has been observed (CTC grade 3 skin rash on Day +6). One patient with progressive NHL prior to transplant received only 3 doses and was removed from the study, and a second patient with primary refractory NHL died of sepsis within two weeks of transplant. Nine patients are fully evaluable for AGVHD (table). All four patients receiving 6 doses of KGF developed AGVHD (one each with overall grades 1 to 4). Of five patients receiving either 12 or 18 doses of KGF, one patient had grade 1 and one had grade 2 AGVHD. Six patients are in remission at last follow-up. These preliminary results at the higher KGF doses compare favorably to historical controls in which the incidence of AGVHD is 50 to 75% in patients receiving unrelated or HLA-mismatched allografts. The study continues to accrue patients and will escalate the administration schedule of KGF up to 36 doses based on the incidence of DLTs.

Age	Diagnosis	Prep	Donor	Cell Source	Doses of KGF	Overall AGVHD	Alive? (Y/N)	# Days after Transplant
29	Refractory NHL	CVB	5/6 URD	BM	3	NE	N	22
16	MDS-NOS	BAC	6/6 URD	BM	6	2	Y	250
42	CML-AP	BAC	5/6 REL	PBSC	6	4	N	22
15	ALL-2nd Relapse	BAC	6/6 URD	BM	6	1	Y	178
58	CML-AP	BAC	6/6 URD	BM	6	3	N	163
58	1°Refractory NHL	CVB	6/6 URD	PBSC	9	NE	N	16
22	ALL-CR2	CyTBI	6/6 URD	PBSC	12	1	Y	208
38	2°MDS	BAC	6/6 URD	BM	12	0	Y	206
22	1°Refractory ALL	CyTBI	6/6 URD	PBSC	18	0	Y	104
36	Ph+ ALL-CR1	CyTBI	6/6 URD	BM	18	2	Y	104
31	MDS/MF	BAC	6/6 URD	PBSC	18	0	Y	67

15

SIROLIMUS (RAPAMYCIN) FOR TREATMENT OF STEROID-REFRACTORY CHRONIC GRAFT VERSUS HOST DISEASE

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Chronic graft versus host disease (cGVHD) occurs in approximately 50% of patients following hematopoietic stem cell transplant. We conducted a phase II trial in 29 patients with steroid-refractory cGVHD (median age 42 years, range 18-69) utilizing tacrolimusin combination with sirolimus. At the time of sirolimus initiation, 20 patients (69%) had extensive cGVHD, and 9 patients limited. Disease sites included: lower GI tract (n=2), liver (n=6), skin (n=24), oral/vaginal mucosae (n=5), ocular (n=3), and upper GI tract (n=1). Eight patients had skin involvement (30%) with scleroderma. The onset of cGVHD at study enrollment included 15 relapsing (52%), 12 progressive (42%), and 2 (7%) de novo cases. All patients had failed multiple previous lines of immunosuppression (median 4, range 2-14) prior to sirolimus. Patients received sirolimus suspension orally at a loading dose of 6 mg, followed by a maintenance dose of 2 mg/day to maintain trough concentrations of 5-15 mg/dl. Additional monitoring included weekly lipid panels, HMG-CoA reductase inhibitors and